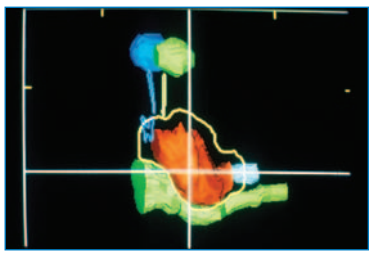
Proton Beam Radiation Therapy: Balancing Evidence-Based Use with the Bottom Line



BY ERIC T. ROSENTHAL

Part 4 of a Series

"There's a huge opportunity to gain with protons even if we can't cure more patients, but I think we will. But even if we didn't, there would still be a huge gain from a financial point of view, not to mention the most important thing—patient quality-of-life issues to reduce morbidity with protons."

Despite the considerable costs and specific-use controversies (especially regarding prostate cancer), proton beam radiation therapy (PBRT) remains a much sought-after technology for certain cancer centers, as well as some institutions that don't even have any direct health care affiliations.

As reported in Part 3 of this series in the April 25th issue, the current PBRT club consists of only seven members providing clinical care with a few other facilities either already under construction or being considered so for the future, often depending more on financing than medical science.

OT requested interviews over several weeks from various institutions to discuss how PBRT was being utilized in today's competitive health care environment

Interestingly some of those centers without the technology declined to discuss the matter at all, as did the granddaddy of proton therapy centers, Loma Linda University Medical Center.

For example, after learning from several sources about a proposed consortium among several prominent academic cancer centers in New York City, I hoped to speak with Simon N. Powell, MD, PhD, Chair of the Department of Radiation Oncology at Memorial Sloan-Kettering Cancer Center (MSKCC), to learn more about the concept—which seemed to be a very cost-effective and collegial attempt at making this expensive technology available to more patients without any single institution incurring the crushing costs—as well as to find out where MSKCC might refer its patients who could benefit from proton therapy.

JAMES D. COX, MD: "Proton therapy's role here [at M. D. Anderson Cancer Center] is for tumors that need a high dose for control that are being treated with curative intent where the surrounding normal tissues are sensitive and where we need to keep the dose as low as possible or to miss those tissues altogether. The main areas we are using protons for now are in cancer of the prostate, non-small-cell carcinoma of the lung, and brain tumors, especially those in children."

Via the Cancer Center's Public Affairs Office, though, Dr. Powell declined to be interviewed, saying that it was too early and premature to discuss either PBRT or the consortium.

Dr. Powell's counterpart at Roswell Park Cancer Institute, Michael R. Kuettel, MD, PhD, MBA, President of the American College of Radiation Oncology (ACRO), also declined, replying through Public Affairs that he was not an expert on proton beam radiation therapy and that any questions regarding ACRO's position would have to be submitted in writing for review by the association's board.

Johns Hopkins Cancer Center said it would not refer any prostate cancer patients for proton therapy, but did send some pediatric sarcoma patients to Massachusetts General Hospital for a specific clinical trial.

I called Jerry D. Slater, MD, Professor and Chairman of the Department of Radiation at Loma Linda, home of the James M. Slater, MD, Proton Treatment and Research Center, named for his father, and operating since 1990. I was told that Dr. Slater was unreachable until more than week after this article was to be submitted, and then asked the public affairs department for another expert. They insisted on a list of specific questions, which I sent, but no one followed up by the deadline.

Baby & Bath Water

In the PBRT article in the April 25th *OT*, Anthony L. Zietman, MBBS, MD, President of the American Society for Radiation Oncology and the Jenot and William Shipley Professor of Radiation Oncology at Harvard Medical School and Director of the Radiation Oncology Residency Program at Massachusetts General Hospital, commented that he was "afraid that the prostate issue will cause proton therapy to be discredited and the baby will be thrown out with the bath water."

He was referring to the lack of any clinical evidence that proton therapy was better than some other more readily available radiation therapies for prostate cancer, and that some centers were treating men for prostate cancer because it was easier and more lucrative and they could handle up to six men in the same time it took to treat a single pediatric patient under anesthesia, a much better candidate for PBRT.

JAY S. LOEFFLER, MD: "Protons produce a better dose distribution compared with x-rays, so if you take the fanciest x-ray dose, protons are always superior. The problem is that there has never been a randomized trial comparing the best of x-rays with the best of protons. Radiation oncology is a funny field because we make decisions about treatment delivery based on computer graphics and a summation of the dose distribution and we adopt new technologies based on improvement of dose distribution."

Dr. Zietman also said that as soon as its $10 million NCI grant was approved, Mass General and the University of Pennsylvania Cancer Center would immediately begin a collaborative randomized clinical trial comparing PBRT with intensity modulated radiation therapy (IMRT) for prostate cancer, with quality of life as the endpoint.

'Very Complicated Question'

Jay S. Loeffler, MD, Chair of Radiation Oncology at Mass General, and the Herman and Joan Suit Professor of Radiation Oncology at Harvard Medical School, called discussing the use of PBRT "a very complicated question—It shouldn't be, but it is," he said.

"Protons produce a better dose distribution compared with x-rays, so if you take the fanciest x-ray dose, then protons are always superior to them. The problem in the field of proton therapy is that there has never been a randomized trial comparing

the best of x-rays with the best of protons. Radiation oncology is a funny field because we make decisions about treatment delivery based on computer-graphics and a summation of the dose distribution and we adopt new technologies based on improvement of dose distribution."

He noted that the FDA requires clinical trials for drug development to show how safe the drug is and how it compares with other available drugs, and that a comparable system does not exist in radiation oncology. "If you have a new technology where the dose distribution is better than other technologies, we assume that it provides better therapy—and it might, but there's no evidence to support it."

He added that many people would now argue that proton therapy will be obviously superior in children because the amount of radiation outside the target volume is reduced, a situation that also reduces the potential late effects in a developing child such as organ function, growth, and risk of second tumors.

"In the pediatric world there is very little debate that protons are a technology that should be associated with better long-term outcomes, but you need about 20 or 30 years of outcomes to prove that.

"There are also subsets of tumors of the eye where proton therapy appears better than any other radiation technology—particularly ocular melanomas where patients can have tumors controlled and can keep useful vision, which would not be feasible if more common types of radiation were used."

And Dr. Loeffler said there is also little argument that patients with certain tumors of the skull base that require enormous controlled doses of radiation would also be better off if treated with protons.

However, he noted that where proton therapy "gets fuzzy" is in treating prostate cancer: "We have not turned this place into a prostate cancer treatment factory like some other proton centers have. We

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treat selective patients on protocol asking questions, but we certainly don't routinely offer all our prostate cancer patients proton therapy."

Dr. Loeffler said that there was also an issue when treating an elderly group of prostate cancer patients who might not have the life span to prove that decreasing the dose outside the prostate makes a substantial difference.

"It might, but we may never be able to prove that, and I think that while we might find that protons are the standard of care for the cancers I've mentioned, we are more dedicated to quantifying the potential gain by designing studies to document potential proven outcomes of protons versus x-rays."

He said that in addition to the proposed randomized clinical trial for prostate cancer with Penn, Mass General was involved in another trial in collaboration with M.D. Anderson that was looking at lung, liver, head and neck, and a variety of pediatric cancers.

Longest Track Record

Mass General has the longest track record using proton beam therapy, going back to 1961, although it was another 40 years before patients could receive treatment in a clinical setting rather than at Harvard University's physics laboratory.

Originally called the Northeast Proton Therapy Center, the facility serves as a regional—as well as national and international—resource for proton therapy, according to Dr. Loeffler, who said that the other Harvard hospitals, including Children's Hospital Boston, Brigham and Women's Hospital, and Dana-Farber Cancer Institute, make referrals to Mass General, as do some out-of-network centers such as Tufts-New England Medical Center.

He said that 20% of Mass General's proton patients were children, but they required 40% of the time, adding, "You really get killed taking kids because they need complicated treatment often requiring anesthesia that takes an enormous amount of time.

"If your proton facility was paid for by investment bankers who want a return, then the last thing they want is to treat a child. We have some kids who take an hour and a half to two hours to treat, and you can treat seven to 10 prostate patients at same time. We don't have a very cost-effective group of patients, but that's okay. Our facility was built half by a grant from NCI [for $26 million], and we have a different mission than they do at some other centers."

Stuart E. Siegel, MD, Director of the Children's Center for Cancer and Blood Diseases at Children's Hospital of Los Angeles and Professor of Pediatrics at the University of Southern California's Keck School of Medicine, said that as far as the use of proton beam technology in pediatric cancer is concerned, "the summary of the current opinions and data is that there is no convincing well-controlled studies that show this technology offers a substantial benefit over the latest conformal radiation therapy techniques in the pediatric population," and that the reasons PBRT may be less toxic for children are only theoretical at this time.

However, he said that in rare cases where the field of radiation is close to a structure that is particularly sensitive to radiation effects and could be destroyed by them—such as in treating soft tissue tumors close to the orbits—he has referred about two or three pediatric patients to Loma Linda during the course of a year.

Last November, St. Jude Children's Research Hospital announced that it was collaborating with the University of Florida's Proton Therapy Institute to begin a proton therapy clinical trial for St. Jude patients younger than three years old with rare brain cancers in an effort to improve response rates and decrease treatment-related side effects.

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The University of Pennsylvania has a memorandum of understanding with ProCure Treatment Centers Inc. to work with the company in technical development, clinical research, and training, and will also be working closely to develop a national registry for cancer patients receiving proton therapy that will help establish standard quality-assurance procedures across the centers.

Future Centers

In addition to the seven currently operating proton beam radiation therapy centers, Leonard Arzt, Executive Director of the National Association for Proton Therapy, noted that ProCure Treatment Centers Inc., a Bloomington, Indiana for-profit company that provides management support and models for the design, construction, operation, and maintenance of proton therapy centers, recently announced the opening of a new facility in Somerset, NJ, in 2012.

He said that there is also discussion about new centers opening in Seattle; southern California; southern Florida; Brooklyn, NY; and Michigan, and that two other planned centers in the greater Philadelphia area, in Michigan and in Illinois had fallen through.

Still River Systems, located in Littleton, Mass., is designing a less-expensive single-room proton beam radiation therapy system scaled for use at cancer centers that want PBRT capability.

However, the system is still not FDA approved, and *OT* learned that a number of institutions that had initially expressed interest in the concept decided not to follow through.

According to Mass General's Jay S. Loeffler, MD, "The thing that has changed in the last three years or so—which I think may be related to the recession and the threat from health care reform—is that I don't get the calls I used to receive about once a week from a dean or a hospital president or investment person saying they want to make money and put in a proton center. It's interesting, it's a huge amount of money to invest, and it's not clear if it's going to make money in the future. In fact it could lose money in the future."

→PBRT
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'Evolving, Not in Fixed Place'

James D. Cox, MD, head of Radiation Oncology and the Hubert L. and Olive Stringer Distinguished Chair in Oncology at M. D. Anderson, said that the center's current view about available technology in proton therapy is that it is evolving and not in a fixed place at this point.

"Proton therapy's role here is for tumors that need a high dose for control that are being treated with curative intent where the surrounding normal tissues are pretty sensitive and where we need to keep the dose as low as possible or to miss those tissues altogether.

"The main areas we are using protons for now are in cancer of the prostate, non-small-cell carcinoma of the lung, and brain tumors—especially those in children, and then brain tumors more broadly."

He said those sites encompass more than 90% of treatment and that occasionally proton therapy might be used for sarcomas that are recurrent in the pelvis or where there is some postoperative residual disease that is near sensitive structures.

Concluding Article

In the next and concluding article in this series: Why and how a university with no medical school, medical center, or cancer center built one of the most expensive proton beam radiation therapy facilities in the world.

Children constitute about 15% of those treated, but Dr. Cox noted that M. D. Anderson treats more than 100 patients daily, and about half of the 15 or so children each day require anesthesia, which takes a lot more time.

"We're receiving pediatric referrals from the United Kingdom, Norway, Canada, and US institutions including Johns Hopkins."

Of the 580 patients treated last year, 310 were for prostate cancer, and all of them were on protocols. "From the very beginning we have taken the viewpoint that we want to deliver proton beam therapy when the indications are clear, and our goal is to expand the indications for proton beam therapy in the proper academic tradition," he said.

"We have the commitment to try to provide the treatment to patients who can be well-served by it, but not just for the sake of treatment but also as a proper academic enterprise."

Dr. Cox said that he was not always a believer in the value of proton therapy and recalled that when he served on NCI's Board of Scientific Advisors he was on a committee in 1989 that was reviewing a proton beam proposal by Mass General: "I didn't have the vision then to think it was that compelling, but by 1998 I had totally come around to recognizing that proton beam therapy could be very useful since the scientific process showed me the value of conformal radiation."

Public-Private Partnership

M. D. Anderson funded its $125 million center through a public-private partnership that included an investment bank, a health care facilities company, public-employee pension systems, and manufacturers of both medical imaging systems and radiation therapy equipment.

The $140 million Roberts Proton Therapy Center at the University of Pennsylvania, which accepted its first patient this January, got an initial $15 million boost from two of its alumni.

Stephen M. Hahn, MD, Chairman of the Department of Radiation Oncology and the Henry K. Pancoast Professor at the University of Pennsylvania School of Medicine, said that all of Penn's proton patients were on protocols.

He noted that patients can benefit from new technologies at the same time institutions advance medical knowledge and money is generated to help further the academic mission.

"I believe that proton therapy will be one of those situations that will help people and in the process be profitable for health systems. Hopefully, it won't bankrupt the system, but it is something that can align patient's interests, research interests, and financial interests."

He cited a Phase II lung cancer clinical trial conducted at M. D. Anderson by Dr. Cox that showed that giving a 15% to 20% higher dosage with protons also simultaneously had a significant reduction in radiation damage to the lungs and esophagus, normally a huge cause of morbidity in patients and a huge cost driver in medicine because patients have to be admitted and receive feeding tubes.

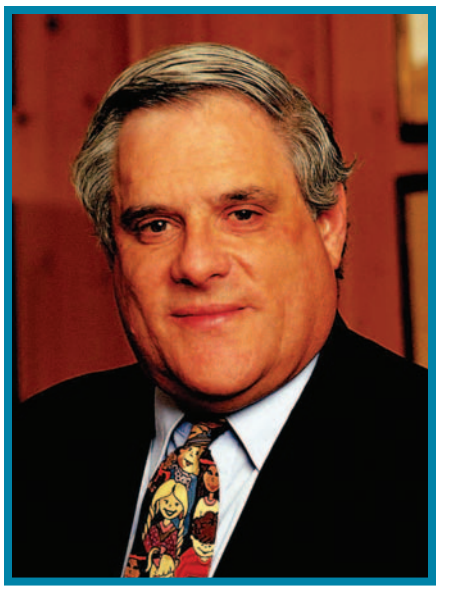
"I actually think there's a huge opportunity to gain with protons even if we can't cure more patients, but I think we will. However, even if we didn't, there would still be a huge gain from a financial point of view, not to mention the most important thing—patient quality-of-life issues to reduce morbidity with protons. I think when we look at this at the end of the day it's going to end up being cheaper to do that."

Dr. Hahn said he looks forward to working with other proton centers to develop protocols, and that Penn has a memorandum of understanding with ProCure Treatment Centers Inc. (*see box*) to work with the company in technical development, clinical research, and training, and will also be working closely to develop a national registry for cancer patients receiving proton therapy that will help establish standard quality-assurance procedures across the centers.

"This will link private practice and academia in a way that has not been done before, and the current proposal is that data will be collected and stored at Penn; it would be independent and not controlled by ProCure; all the doctors involved would have access to it; and we would be able to publish our outcomes in a meaningful way."

He emphasized that Penn is not a ProCure facility, and that although James M. Metz, MD, Vice Chair for Clinical Operations in his Department of Radiation Therapy is a medical advisor to ProCure, Dr. Metz is not involved in any discussions between Penn and ProCure.

The institution has also created the Penn Proton Priority System, he noted, a multidisciplinary group that meets weekly to select patients for proton therapy based on scored and weighted factors to determine the best candidates.



STUART E. SIEGEL, MD, said that the summary of current opinions and data is that there is no convincing well-controlled studies that show that proton beam radiation therapy offers a substantial benefit over the latest conformal radiation therapy techniques in the pediatric population, and that the reasons PBRT may be less toxic for children remain only theoretical at this time.